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Case report

Fatal idiopathic pulmonary haemosiderosis in association with pregnancy – Medico-legal evaluation

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ABSTRACT

Idiopathic pulmonary haemosiderosis is a rare disorder characterised by repeated episodes of intra-alveolar bleeding in association with consecutive anaemia, pulmonary fibrosis, pulmonary hypertension and respiratory failure. Pregnancy may exacerbate the symptoms of idiopathic pulmonary haemosiderosis typically worsening in the third trimester. A 32-year-old female after delivery was admitted to hospital with progressive dyspnoea of about 1-month duration. Sudden circulatory collapse caused fatal complication. During the post-mortem investigation, lung haemorrhage and histologically abundant iron deposition in macrophages and interstitial fibrosis were found. Medico-legal post-mortem evaluation of fatal cases may support the clinico-pathological context of the diagnosis of this entity.

1. Introduction

Idiopathic pulmonary haemosiderosis (IPH) is a very rare disorder of unknown aetiology characterised by recurrent or chronic episodes of alveolar haemorrhage and accumulation of haemosiderin in the lung parenchyma.[1,2] The incidence of IPH is unknown; however, studies suggest that it lies between 0.24 and 1.23 cases per million live births per year.[3] Clinical manifestations of IPH include iron-deficiency anaemia without any known cause, pulmonary symptoms such as haemoptysis, progressive dyspnoea and cough and parenchyma lesions.[1] IPH over time leads to progressive secondary pulmonary fibrosis, pulmonary hypertension and cor pulmonale. It is a disease of childhood and usually occurs in children before 10 years of age; however, it could occur in young adults. Females with IPH rarely survive to childbearing age or are unable to become pregnant.[3] IPH has rarely been reported in pregnancy[4,5]; however, pregnancy may exacerbate the symptoms of IPH with the symptoms typically worsening in the third trimester.[6–8] Death may occur suddenly from acute pulmonary haemorrhage or progressive respiratory failure.[9] Post-partum complications have a great public interest and require medico-legal evaluation.

We report a case of a young woman with fatal IPH after pregnancy due to acute pulmonary haemorrhage.

2. Case report

2.1. History

A 32-year-old female was admitted to hospital with progressive dyspnoea of 1-month duration starting straight after delivery. Pregnancy was uncomplicated except for slight gynaecologic infection treated with antibiotic. Her symptoms started with chest pain and fever without any typical alteration on a chest computer tomogram. Antibiotic treatment resulted in temporary clinical remission; however, later, progressive effort dyspnoea started. By the time of her hospital admission, she had pulmonary hypertension (pulmonary arterial pressure (PAP) 67–93 mmHg) and respiratory failure with severe hypoxaemia (arterial blood gas: alveolar oxygen pressure (PaO_2): 6.84 kPa; arterial oxygen saturation (SaO_2) 89% during 3 l min^{-1} oxygen supplementation), and there was no experience of haemoptysis. A computer tomogram–pulmonary

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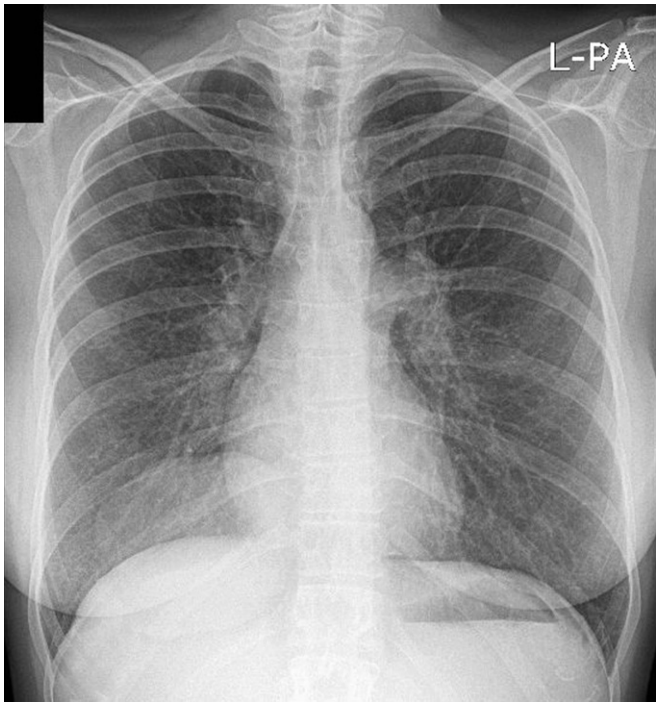

Fig. 1. Chest X-ray shows right-sided pleural effusion with sharp margin above the diaphragm. In the right lower lobe there are opacities caused by compressed parenchyma. Hilum is slightly enlarged due to dilated pulmonary artery.

angiogram demonstrated no evidence of thrombo-embolism, and confirmed bilateral pleural effusion, transitory pulmonary infiltrate and very slight parenchyma opacities; and right hilar lymphadenopathy were noted on chest X-ray (Fig. 1).

During observation, an acute episode with chest pain, haemoptysis and deterioration of her respiratory and radiology status occurred. Laboratory analysis did not support anaemia. Bronchoscopy was performed and revealed normal airways with some blood leakage from right lower lobe. Analysis of broncho-alveolar lavage fluid was not diagnostic; the patient's respiratory status did not allow for trans-bronchial lung biopsy. Immunological evaluation did not support antineutrophil cytoplasm antibodies (ANCAs) or anti-glomerular basement membrane antibodies' (anti-GBMs) positivity; however, other auto-immunity affecting lungs could not be completely excluded. Improvement of tissue oxygenation and decline of PAP (PAP 46 mmHg, PaO_2: 8.17 kPa; SaO_2 93% during 1.5 l min^{-1} oxygen supportation) was obtained, supported by high-dose methylprednisolone therapy. Lung biopsy could be indicated in case of improvement of clinical status. The second acute relapse of disease led to a sudden collapse of her circulation with unavailable resuscitation.

2.2. Autopsy findings

A complete forensic autopsy was performed. On opening the thoracic cavity, there was 1100 ml blood-tinged fluid in the right pleural cavity. Lungs weighed 2100 g, and a massive circumscribed haemorrhage – 10 cm in diameter – was observed in the right lower lobe and in the lower margin of upper lobe. The pleura was dull, opaque, and thickened. In the parenchyma, several haemorrhagic focuses 0.5–3 cm in diameter were detected around the circumscribed dark area (Fig. 2). The pulmonary vessels were dilated and could be traced to the sub-pleural surface. The heart weighed 290 g, and there was marked dilatation of the right atrium, right ventricular cavity and pulmonary trunk. Other internal organs showed hypoxic changes.

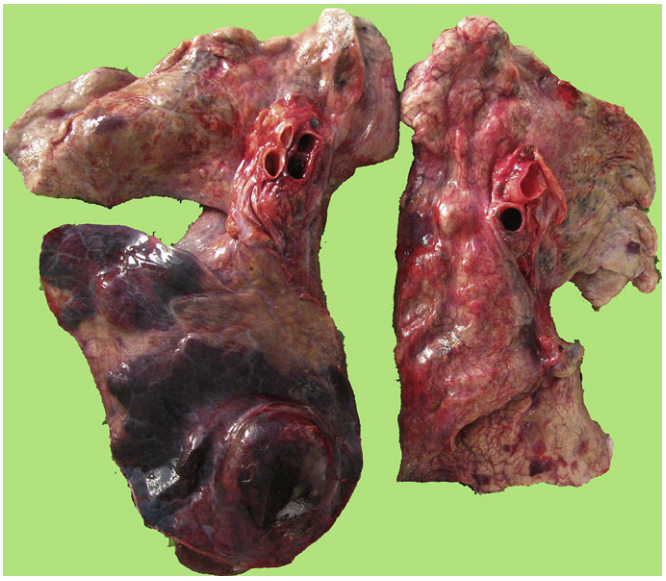

Fig. 2. Gross photograph showing a large and several smaller pulmonary hemorrhages in the right lung.

2.3. Histopathology

Tissue specimens from every internal organ were fixed in paraformaldehyde, embedded in paraffin and stained by haematoxylin–eosin (HE) and Prussian blue (haemosiderin-bound unreactive Fe^{3+}) procedures. Microscopically, thickening of pleura and alveolar walls was revealed and a severe interstitial fibrosis was observed. Haemosiderin-laden macrophages filled the compressed alveolar spaces, and in some areas a few iron-laden macrophages were detected also in thickened alveolar septa (Fig. 3(A) and (B)). In other internal organs, no iron deposition was found.

3. Discussion

In this report, we presented a case of a young woman who had post-partum pulmonary symptoms, and died suddenly by the

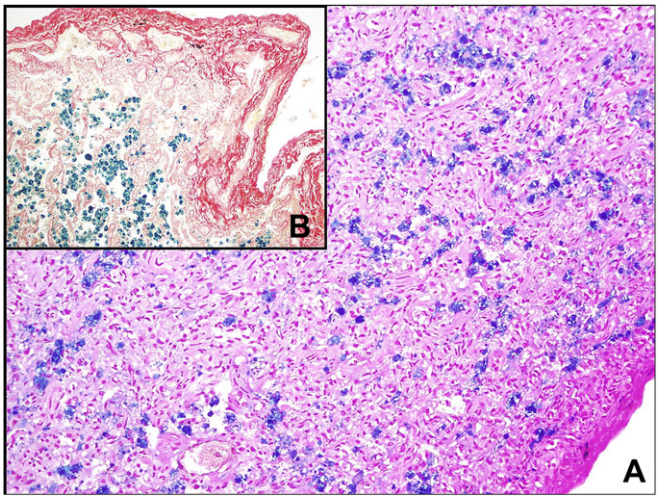

Fig. 3. A,B – Idiopathic pulmonary hemosiderosis. Fibrosis of the lung and Prussian blue positive pigment containing macrophages in alveoli (×200). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

complications of a huge pulmonary haemorrhage in connection with IPH. Based on the sudden death of the young female during medical treatment, medico-legal autopsy was indicated. IPH is a rare condition, and to date, about 500 cases have been reported in the literature.[9] Although IPH may be associated with an immunological,[1,10] genetic[11] or toxic[12] mechanism, the exact aetiological mechanisms remain unknown.[7,13] Pathologically, IPH is characterised by heavy lungs with aggregates of haemosiderin-laden macrophages due to recurrent diffuse alveolar haemorrhage in the absence of vasculitis or capillaritis and by eventual interstitial fibrosis.[14]

Pregnancy could also exacerbate the symptoms of IPH, necessitating early delivery.[3] Continued increase in cardiac output and pulmonary blood flow was observed in the third trimester of pregnancy, unmasking subclinical pulmonary haemorrhage.[8] These changes are poorly tolerated by patients with secondary pulmonary hypertension and can lead to the development of acute right heart failure and rapid cardiovascular decompensation. Maternal death or sudden unexpected death in a short time after delivery has a great professional and public interest in every developed country. Careful post-mortem investigation and evaluation of diagnostic procedures may support clinical management of the disease. In pregnancy, the reduction in maternal systemic vascular resistance and a reduction in umbilical artery blood flow predispose to foetal intrauterine growth retardation.[15]

Clinically, IPH has a triad manifestation of haemoptysis, diffuse parenchyma infiltration on chest radiography and iron-deficiency anaemia.[9] In IPH patients death may occure suddenly and unexpectedly.[16] Laboratory and radiologic findings that have been found to be helpful to diagnose the disease are anaemia, chest X-ray showing minimal transient infiltrates to massive parenchymal involvement with secondary atelectasis, emphysema and hilar lymphadenopathy. In IPH the pulmonary function tests may show interstitial lung disease and increase in single breath CO uptake.[17] However, the study result demonstrated that blood cell count and chest X-ray findings were not statistically different between haemosiderosis patients and others. Chest radiography may reveal diffuse infiltration.[2] Examination of the broncho-alveolar lavage fluid can disclose haemosiderin-laden alveolar macrophages, and the lung biopsy shows numerous siderophages in the alveoli and even pulmonary fibrosis at the late stage.[18]

There have been reports of IPH occurring in individuals with coeliac disease, pointing to a possible auto-immune aetiology of IPH.[10] This extremely rare combination of IPH and coeliac disease was first described in 1971 by Lane and Hamilton.[19] Coeliac disease has been observed to result from an inappropriate T-lymphocyte-mediated immune response against ingested gluten in genetically predisposed individuals.[20] Three pathogenic hypotheses are discussed in the literature to explain the association of IPH and coeliac disease: deposition of circulating immune complexes involving food allergens on the basement membrane of alveolar capillaries; reaction between autoantibodies against reticulin and alveolar basement membrane antigen; and an effect of adenovirus 12, a potential causative factor for coeliac disease.[21] In cases of Lane–Hamilton syndrome, the introduction of a gluten-free diet is sufficient for complete remission of IPH, which seems to prove the common immunological mechanism.[22] The relapse of both IPH and coeliac disease symptoms in the patient who stopped the gluten-free diet supports a gluten-dependent mechanism for IPH.[21]

Improved understanding of the pathophysiology of IPH may impact the role of the forensic pathologist. In conclusion, the management of pregnant patients with IPH should be multidisciplinary. Prenatal investigations to determine the nature of their respiratory disease and any other co-morbidity should be emphasised. Based on the case reported herein, we suspect that a diagnosis of IPH could be made with great importance in pregnancy or the post-partum period. Forensic aspects of medical malpractice, diagnostic failure and negligence were carefully evaluated. During the hospital treatment, all the clinical aspects, results of laboratory tests and computer tomogram and anamnestic data were considered for the diagnostic consequences. However, the clinical diagnosis was not correct; the rarity of IPH, the severe fatal complication and the complexity of diagnostic procedures supported the final forensic expert opinion that this case was not a malpractice case, and there were no further legal consequences from the fatality reported. We can summarise our findings as medico-legal post-mortem evaluation of fatal cases may support the clinico-pathological context of the diagnosis and management of the delivery.

Conflict of interest

None declared.

Funding

None declared.

Ethical approval

None declared.

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